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(57) Abstract

Ophthalmic compositions and methods for preserving and using such compositions are disclosed. In one embodiment, such compositions include a liquid medium, a first antimicrobial component selected from antimicrobial peptides and mixtures thereof, and a second antimicrobial component, other than the first antimicrobial component, which is preferably substantially non-oxidative. Compositions which include a liquid medium and antimicrobial peptide nanotubes effective to disinfect a contact lens present in the liquid medium containing the nanotubes are also disclosed. Preserved compositions useful for caring for contact lenses are included within the scope of the present invention.

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OPHTHALMIC COMPOSITIONS INCLUDING PEPTIDES AND PEPTIDE DERIVATIVES AND METHODS FOR USING SAME

Background of the Invention

This invention relates to ophthalmic compositions and methods for preserving and using such compositions. More particularly, the present invention relates to ophthalmic compositions, for example, useful in caring for contact lenses, which include one or more peptides and/or peptide derivatives as antimicrobial agents, and to methods for using such compositions, for example, to care for contact lenses.

Various compositions, such as solutions, are used in association with contact lenses to ensure that the lenses may be safely, comfortably and conveniently worn. Contact lens care compositions, for example, disinfecting compositions, cleaning compositions, wetting compositions, conditioning compositions and the like, often utilize at least one disinfectant or preservative, depending on the type of composition, for disinfecting contact lenses after wear or for preserving the lens care composition itself.

A contact lens disinfecting composition generally has sufficient antimicrobial activity so that when the composition is contacted with a contact lens to be disinfected, microorganisms associated with the lens are killed or otherwise removed and the contact lens is effectively disinfected within a reasonable time, for example, in the range of about 0.1 hour to about 12 hours. A contact lens disinfecting composition may be termed a microbicidal composition. In contrast, a preserved contact lens care composition has sufficient antimicrobial activity, often less of such activity than is present in a contact lens disinfecting composition, so that when the composition is contacted with a contact lens substantially no increase in the microorganism population on the lens or in the composition is obtained. A preserved contact lens

care composition may be termed a microbiostatic composition. Contact lens care compositions are often preserved to prevent any substantial increase in, or to gradually decrease, the population of contaminating microorganisms in the compositions and, thereby, to extend their shelf life. Some preservatives used in preserved compositions may also be used as disinfecting agents in contact lens disinfecting compositions.

Various compounds are known for use as preserving agents in preserved contact lens care compositions. Examples include thimerosal, benzalkonium chloride and chlorhexidine. However, these preserving agents are known to exhibit ocular toxicity which may result in irritation or sensitivity to the eye. The degree of ocular toxicity increases when these agents are utilized as disinfecting agents. Further, a soft contact lens, a rigid gas permeable contact lens (RGP) or a hard contact lens can absorb or adsorb these compounds. This causes the contact lens to retain the irritating compound and contributes to the eye irritation and sensitivity which may result.

Other conventional methods of contact lens chemical disinfection utilize one or more active disinfecting agents in an aqueous medium, for example a chlorhexidine/thimerosal solution or a relatively mild solution of hydrogen peroxide. Some of these disinfecting solutions, such as those named above, are cytotoxic and are known to be adsorbed or absorbed onto or into a contact lens and cause the lens to elicit a cytotoxic response after disinfection. For example, contact lenses which have been soaked in a disinfecting hydrogen peroxide solution are to be treated to remove residual hydrogen peroxide, e.g., by soaking in a catalase solution, before they may be comfortably and safely worn again. If residual hydrogen peroxide remains on the lenses, then irritation to the eye may result.

Thus, it is readily apparent that a continuing need exists for safe and efficacious compositions that can be used as contact lens disinfecting compositions and as preserved contact lens care compositions.

Summary of the Invention

New disinfecting and preserved compositions and methods employing such compositions, particularly compositions and methods directed to contact lens care, have been discovered. The present compositions include effective disinfectants and/or preservatives. Thus, for example, a contact lens can be effectively disinfected in a reasonable length of time. Also, contact lens care products can be effectively preserved against growth of contaminating microorganisms. Importantly, such disinfecting and preserving activities are achieved, and the contact lenses disinfected or otherwise cared for using the present compositions can be safely and comfortably worn with little or no risk of eye irritation or sensitivity.

In one broad aspect of the invention, compositions useful for disinfecting a contact lens are provided. Such compositions comprise a liquid medium, preferably an aqueous liquid medium; a first antimicrobial component selected from the group consisting of antimicrobial peptides and mixtures thereof; and a second antimicrobial component other than the first antimicrobial component. The first and second antimicrobial components together are present in an amount effective to disinfect a contact lens contacted with the composition.

In another broad aspect of the present invention, compositions useful for treating a contact lens are provided. These treating compositions comprise a liquid medium, preferably a liquid aqueous medium; a first antimicrobial component selected from the group consisting of antimicrobial peptides and mixtures thereof; and a

second antimicrobial component other than the first antimicrobial component. The first and second antimicrobial component together are present in an amount effective to preserve the composition.

An additional aspect of the present invention involves compositions useful for disinfecting a contact lens which comprise antimicrobial peptide nanotubes. The antimicrobial peptide nanotubes are present in an amount effective to disinfect a contact lens in a liquid medium containing such nanotubes. In addition, these compositions preferably include a destroying component effective to destroy peptide nanotubes in an amount effective to destroy all the antimicrobial peptide nanotubes present in the compositions.

Methods for disinfecting contact lenses and for caring for contact lenses using the present compositions are also provided and are included within the scope of the present invention.

Detailed Description of the Invention

The present invention is applicable to disinfecting or otherwise caring for all types of lenses, for example, contact lenses, which are benefitted by such disinfecting or other caring. Such lenses, for example, conventional soft contact lenses, RGPs and hard contact lenses may be made of any suitable material or combination of materials and may have any suitable configuration. The invention is also applicable to preserve compositions, such as contact lens care compositions and other eye care compositions, which are benefitted by being preserved.

One important feature of the compositions of the present invention is the inclusion of one or more antimicrobial peptides in contact lens disinfecting compositions and preserved contact lens care compositions.

In one embodiment, the present compositions include a sufficient amount of antimicrobial peptide nanotubes to

effectively disinfect contact lenses contacted with the nanotube-containing compositions. In another embodiment, the present compositions include a liquid medium, a first antimicrobial component selected from the group consisting of antimicrobial peptides, preferably other than peptide nanotubes, and mixtures thereof; and a second antimicrobial component other than the first antimicrobial component, which second antimicrobial component is preferably substantially non-oxidative. The first and second antimicrobial components together are present in an amount effective to disinfect a contact lens contacted with the composition. In these compositions, the amounts of the individual first and second antimicrobial components included is preferably reduced relative to using only one of the antimicrobial components to perform the disinfecting. Thus, the reduced amounts of first and second antimicrobial components reduce the risk of eye irritation. Alternately, enhanced antimicrobial activity is obtained if disinfecting amounts of both first and second antimicrobial components are included in the compositions.

The present compositions may further include a destroying component, more preferably selected from proteolytic enzymes, for example, proteases, and mixtures thereof, effective to destroy or degrade peptides, for example, peptide nanotubes, in an amount effective to destroy or degrade all the antimicrobial peptides present in the compositions. Antimicrobial peptide nanotubes, although being very useful in the present compositions and methods, are believed to have a relatively high potential for causing irritation to ocular tissue. For this reason, if such nanotubes are employed, it is preferred that a destroying component be also used so that the contact lens is freed of the nanotubes prior to being placed into the eye, for safe and comfortable wear.

Peptide nanotubes can be considered stacks of peptide rings. For example, cyclic peptide structures made up of a substantially even number of alternating D- and L- amino acid residues can adopt a substantially flat ring-like conformation and stack, under conditions favorable for such stacking, to produce a hollow tubular structure of sufficient length to span the thickness of the cell membranes of microorganisms. Without wishing to limit the invention to any particular theory of operation, it is believed that such hollow tubular structures are effective to penetrate the cell membranes of microorganisms to form ion-transport pores or channels therein. These pores or channels compromise the cellular and/or ionic integrity and/or stability of the microorganisms sufficiently to kill the microorganisms. Preferably, the hollow tubular structure employs hydrogen bonding to at least partially, preferably substantially totally, maintain the desired tubular structure.

The peptide nanotubes are preferably made from synthetic, rather than naturally-occurring, peptide sub-units. The peptide sub-units should preferably partition favorably into a hydrophobic phase, such as is the case with many channel-forming naturally occurring peptides, and, in addition, are preferably able to participate in extended hydrogen-bonded stacking interactions to produce channel (tubular) structures long enough to span the cell membranes of the microorganisms to be attacked.

A specific peptide sub-unit which may be employed is the cyclic peptide, cyclo[-(Trp-D-Leu)$_3$Gln-D-Leu-], which is composed of alternating L-tryptophan and D-leucine side-chain moieties, with the exception of one L-glutamine residue. This peptide can be made by the conventional solid phase technique (see Merrifield, J. Am. Chem. Soc. 85, 214999-2154 (1963); Barany et al, The Peptides, vol.

2, pp. 1-284 (Gross et al, eds., Academic, New York 1979); and Rovera et al, Tetrahedron Lett, vol. 32, pp. 2639-2642 (1991), each of which is incorporated in its entirety by reference.

The antimicrobial peptides other than the antimicrobial peptide nanotubes useful according to the present invention include synthetic antimicrobial peptides and forms of naturally occurring antimicrobial peptides, preferably cytolytic peptides. Such peptides may be the L-form, the D-form or combinations or mixtures of both forms.

Among the antimicrobial peptides preferably employed are those selected from defensins, peptides related to defensins, cecropins, peptides related to cecropins, magainins, peptides related to magainins and mixtures thereof.

Particularly preferred are the cecropins, magainins and defensins. Exemplary cecropins include the peptides having the following amino acid sequences:

cecropin A:

Lys Trp Lys Leu Phe Lys Lys Ile Glu Lys
Val Gly Gln Asn Ile Arg Asp Gly Ile Ile
Lys Ala Gly Pro Ala Val Ala Val Val Gly
Gln Ala Thr Gln Ile Ala Lys;

and cecropin B:

Lys Trp Lys Val Phe Lys Lys Ile Glu Lys
Met Gly Arg Asn Ile Arg Asn Gly Ile Val
Lys Ala Gly Pro Ala Ile Ala Val Leu Gly
Glu Ala Lys Ala Leu Gly.

Cecropin D can also be employed.

Cecropin derivatives having C-terminus modifications, substitutions, and/or truncations which either enhance or do not inhibit antimicrobial activity are also contemplated for use according to the present invention. Useful derivatives include cecropin A amide (CA-NH_2), and cecropin A with a C-terminal ethylenediamine-modified homoserine (CA-Hse-NH-Et-NH_2). The general sequence homology of the N-terminus portion of the cecropins is necessary for activity and is therefore less suitable for truncation, modification, or substitution. However, analogues resulting from substitution of amino acids with similar chemical characteristics to the original can be designed. Maintaining an amphipathic helical structure similar to the original peptide will result in conservation of antimicrobial activity. An example of a substitution analogue of cecropin B is Shiva-1:

Met Pro Arg Trp Arg Leu Phe Arg Arg Ile
Asp Arg Val Gly Lys Gln Ile Lys Gln Gly
Ile Leu Arg Ala Gly Pro Ala Ile Ala Leu
Val Gly Asp Ala Arg Ala Val Gly.

Shiva-1 and other cecropin substitution analogs having antimicrobial activity are contemplated as being useful according to the invention.

Exemplary useful magainins include the native form, magainin 2. Useful derivatives include magainins having N-terminal positively charged chain extensions (e.g., $(Lys)_{10}$-magainin 2) and C-terminal amide groups (e.g., magainin 2-NH_2) which enhance the antimicrobial activity of the peptides. Additional magainins and magainin derivatives which are contemplated for use according to the present invention are described in Zasloff et al., Proc. Natl. Acad. Sci. USA 85, 910-913 (February 1988);

Zasloff, Proc. Natl. Acad. Sci. USA 84, 5449-5453 (August 1987); and Bessale et al, Antimicrobial Agents and Chemotherapy 36 (No. 2), 313-317 (February 1992), ("Bessale II") each of which is incorporated in its entirety herein by reference.

Defensins useful according to the invention include: HNP-1 (human neutrophil peptide 1):

Ala Cys Tyr Cys Arg Ile Pro Ala Cys Ile
Ala Gly Glu Arg Arg Tyr Gly Thr Cys Ile
Tyr Gln Gly Arg Leu Trp Ala Phe Cys Cys;

HNP-2:

Cys Tyr Cys Arg Ile Pro Ala Cys Ile Ala
Gly Glu Arg Arg Tyr Gly Thr Cys Ile Tyr
Gln Gly Arg Leu Trp Ala Phe Cys Cys;

HNP-3:

Asp Cys Tyr Cys Arg Ile Pro Ala Cys Ile
Ala Gly Glu Arg Arg Tyr Gly Thr Cys Ile
Tyr Gln Gly Arg Leu Trp Ala Phe Cys Cys;

NP-1 (rabbit neutrophil peptide 1):

Val Val Cys Ala Cys Arg Arg Ala Leu Cys
Leu Pro Arg Glu Arg Arg Ala Gly Phe Cys
Arg Ile Arg Gly Arg Ile His Pro Leu Cys
Cys Arg Arg;

and the BNP-1 (bovine neutrophil peptide) sequence:

Arg Leu Cys Arg Val Val Ile Arg Val Cys
Arg.

Other defensins and defensin analogs, such as those described in Selsted et al, J. Clin. Invest. 76, 1436-1439 (October 1985), and Kagan et al, Proc. Natl. Acad. Sci. USA 87, 210-214 (January 1990), each of which is incorporated in its entirety herein by reference, are also useful in the present invention.

The defensins are nonhelical pore formers, unlike the magainins and cecropins. However, analogues which mimic essential aspects of the native peptide conformation (assumed to be antiparallel beta-sheet) are preferred. Therefore, proper pairing and disulfide bonding of cysteine residues is desirable to ensure that the peptide is folded into the appropriate channel forming conformation.

Tachyplesins, such as tachyplesin I and II, and polyphemusins, such as polyphemusin I and II, are defensin-like peptides. See, e.g., Ohta et al, Antimicrobial Agents and Chemotherapy 36 (No. 7), 1460-1465 (July 1992), which is incorporated in its entirety herein by reference. These peptides and antimicrobially active derivatives thereof are also contemplated as being useful in the present invention.

Other peptides, such as hybrids (peptides comprised of sequences from several antimicrobial classes), e.g., cecropin-melittin hybrids, and peptide analogs in which one or more of the L-amino acids are replaced with other L-amino acids, can also be used with advantage provided that they retain sufficient antimicrobial activity.

Exemplary hybrid peptides include cecropin A-(1-8)-melittin-(1-18)-NH_2:

Lys Trp Lys Leu Phe Lys Lys Ile Gly Ile
Gly Ala Val Leu Lys Val Leu Thr Thr Gly
Leu Pro Ala Leu Ile Ser-NH_2;

and cecropin A-(1-3)-melittin-(1-13)-NH_2:

Lys Trp Lys Gly Ile Gly Ala Val Leu Lys
Val Leu Thr Thr Gly Leu-NH_2.

Melittin itself, however, is unsuitable for use due to its high toxicity.

The antimicrobial agents must be compatible with the contact lens being disinfected. The antimicrobial peptides should also be non-toxic to humans.

Antimicrobial agents useful according to the invention can be prepared using techniques well known to those skilled in the art. Antimicrobial peptides can be prepared by the solid-phase synthesis technique noted previously. Exemplary processes for preparing antimicrobial peptides are given in Wade et al, Proc. Natl. Acad. Sci. USA 87, 4761-4765 (June 1990), and Bessale et al, FEBS Letters 274, no. 1,2, 151-155 (November 1990), each of which is incorporated herein in its entirety by reference.

The second or other antimicrobial component employed in the present invention is other than the first antimicrobial component and preferably is other than antimicrobial peptide nanotubes. This second antimicrobial component is more preferably selected from synthetic polymeric antimicrobial components and mixtures thereof.

As used herein, substantially non-oxidative antimicrobial components include effectively non-oxidative organic chemicals, for example, synthetic polymers, which derive their antimicrobial activity through a chemical or physiochemical interaction with the microbes or microorganisms. Suitable non-oxidative antimicrobial components include, but are not limited to, quaternary

ammonium salts used in ophthalmic applications such as poly[dimethylimino-2-butene-1,4-diyl] chloride, alpha- [4-tris(2-hydroxyethyl) ammonium]-dichloride (chemical registry number 75345-27-6, available under the trademark polyquarternium 1® from ONYX Corporation), benzalkonium halides, and biguanides such as salts of alexidine, alexidine-free base, salts of chlorhexidine, hexamethylene biguanides and their polymers, antimicrobial polypeptides, and the like and mixtures thereof. A particularly useful substantially non-oxidative antimicrobial component is selected from polyhexamethylene biguanide (PHMB), N-alkyl-2-pyrrolidone, chlorhexidine, polyquaternium-1, hexetidine, bronopol, alexidine, ophthalmically acceptable salts thereof and mixtures thereof.

The salts of alexidine and chlorhexidine can be either organic or inorganic and are typically disinfecting gluconates, nitrates, acetates, phosphates, sulphates, halides and the like. Generally, the hexamethylene biguanide polymers, also referred to as polyaminopropyl biguanide (PAPB), have molecular weights of up to about 100,000. Such compounds are known and are disclosed in Ogunbiyi et al U.S. Patent No. 4,758,595, the disclosure of which is incorporated in its entirety herein by reference.

The substantially non-oxidative antimicrobial components useful in the present invention are preferably present in the liquid aqueous medium in concentrations in the range of about 0.000005% or about 0.00001% to about 2% (w/v).

More preferably the substantially non-oxidative antimicrobial component is present in the liquid aqueous medium at an ophthalmically acceptable or safe concentration such that the user can remove the disinfected lens from the liquid aqueous medium/matrix

material combination and thereafter directly place the lens in the eye for safe and comfortable wear.

When a contact lens is desired to be disinfected, an amount of disinfectant effective to disinfect the lens is used. Preferably, such an effective amount of the disinfectant reduces the microbial burden on the contact lens by one log order in three hours. More preferably, an effective amount of the disinfectant reduces the microbial load by one log order in one hour. Particularly preferred are disinfectant concentrations that reduce the microbial load by one log order in ten minutes or less.

The disinfectant of the present invention is preferably provided in a liquid aqueous medium. The actual concentration of disinfectant selected depends, for example, on the effectiveness of the specific disinfectant in reducing the microbial load on the contact lens.

The liquid media used are selected to have no substantial deleterious effect on the lens being treated, or on the wearer of the treated lens. The liquid media are constituted to permit, and even facilitate, the instant lens treatment or treatments. The liquid media are preferably aqueous-based and more preferably are substantially isotonic and/or are ophthalmically acceptable liquid aqueous media. A material is said to be "ophthalmically acceptable" when it is compatible with ocular tissue, that is causes no significant or undue detrimental effect when brought into contact with ocular tissue.

The liquid media preferably include an effective amount of a tonicity adjusting component to provide the liquid media with the desired tonicity. The liquid aqueous media of the present invention preferably include a buffer component which is present in an amount effective to maintain the pH of the medium in the desired range. This buffer component may be present in the liquid medium

and/or may be introduced into the liquid medium. Among the suitable buffer components or buffering agents that may be employed are those conventionally used in contact lens care products. The buffer salts are preferably alkali metal, alkaline earth metal, or ammonium salts. Particularly useful media are those derived from saline, e.g., a conventional saline solution, or a buffered saline solution. In addition, the liquid aqueous media may include one or more other materials, for example, as described elsewhere herein, in amounts effective to treat the contact lens (for example, provide a beneficial property to the contact lens) contacted with such media.

The destroying component may be selected from any material or combination of materials useful to destroy or degrade, that is render innocuous, for example, innocuous to ocular tissue, the antimicrobial peptides, for example, the antimicrobial peptide nanotubes. One of the advantages of using compositions comprising antimicrobial peptides and second or other antimicrobial components is that reduced concentrations of both materials may be employed while still providing the desired antimicrobial activity. Using a reduced concentration of antimicrobial peptides reduces the risk of irritating the eye. However, to reduce this risk even further, it is advantageous to employ a destroying component, as described herein, in an amount effective to destroy all the antimicrobial peptides, including such peptides other than the antimicrobial peptide nanotubes, present. Such compositions and methods for using such compositions are within the scope of the present invention.

In a particularly useful embodiment, the destroying component is selected from the group consisting of proteolytic enzymes, for example, proteases, and mixtures thereof. Exemplary proteases are described in Huth et al U.S. Patent No. 32,672RE and Karageozian et al U.S. Patent

No. 3,910,296, which disclosures are incorporated herein by reference.

In one embodiment, a cleaning enzyme component, for example, a proteolytic enzyme component, can be used to remove debris from the contact lens and, in addition, can be used as a destroying component to destroy the antimicrobial peptide nanotubes and/or antimicrobial peptides being employed, when such destruction is desired.

Preferred proteolytic enzymes are those which are substantially free of sulfhydryl groups or disulfide bonds. Metallo-proteases, those enzymes which contain a divalent metal ion such as calcium, magnesium or zinc bound to the protein, may also be used.

A more preferred group of proteolytic enzymes are the serine proteases, particularly those derived from Bacillus and Streptomyces bacteria and Aspergillus molds. Within this grouping, the still more preferred enzymes are the derived alkaline proteases generically called subtilisin enzymes. Reference is made to Keay, L., Moser, P.W. and Wildi, B.S., "Proteases of the Genus Bacillus". II. Alkaline Proteases, "Biotechnology and Bioengineering", Vol. XII, pp 213-249 (1970, March) and Keay, L. and Moser, P.W., "Differentiation of Alkaline Proteases form Bacillus Species" Biochemical and Biophysical Research Comm., Vol 34, No. 5, pp 600-604, (1969).

The subtilisin enzymes are broken down onto two sub-classes, subtilisin A and subtilisin B. In the subtilisin A grouping are enzymes derived from such species as B. subtilis, B. licheniformis and B. pumilis. Organisms in this sub-class produce little or no neutral protease or amylase. The subtilisin B sub-class is made up of enzymes from such organisms as B. subtilis, B. subtilis var. amylosacchariticus, B. amyloliquefaciens and B. subtilis NRRL B3411. These organisms produce neutral proteases and amylases on a level about comparable to their alkaline

protease production. One or more enzymes from the subtilisin A sub-class are particularly useful.

In addition other preferred enzymes are, for example, pancreatin, trypsin, collagenase, keratinase, carboxylase, aminopeptidase, elastase, and aspergillo-peptidase A and B, pronase E (from S. griseus) and dispase (from B. polymyxa).

An effective amount of proteolytic enzyme is preferably used in the practice of this invention. Such amount will be that amount which effects removal in a reasonable time (for example about 4 hours to overnight) of substantially all protein-based or proteinaceous deposits from a contact lens due to normal wear. This standard is stated with reference to contact lens wearers with a history of normal pattern of protein accretion, not the very small group who may at one time or another have a significantly increased rate of protein deposit such that cleaning is recommended every day, or every two or three days.

The amount of enzyme required to make an effective cleaner will depend on several factors, including the inherent activity of the enzyme, and the excipient it contains.

As a basic yardstick, the working solution should contain sufficient enzyme to provide about 0.001 to about 3 Anson units of activity, preferably about 0.01 to about 1 Anson units, per single lens treatment. Higher or lower amounts may be used.

Enzyme activity is pH dependent. Thus, for any given enzyme, there is a particular pH range in which that enzyme will function best. The determination of such range can readily be done by known techniques.

One or more additional components can be included in the present compositions based on the particular application for which the compositions are formulated.

Thus, the present compositions can be formulated as disinfecting compositions, cleaning compositions, wetting compositions, conditioning compositions, soaking compositions and the like. Also, the present compositions can be formulated to be useful in performing two or more contact lens care operations. For example, a disinfecting/cleaning composition, or a cleaning/conditioning composition or even an all purpose lens care composition can be formulated and such multi-functional compositions are included within the scope of the present invention.

The additional component or components included in the present compositions are chosen to impart or provide at least one beneficial or desired property to the compositions. Such additional components may be selected from components which are conventionally used in one or more contact lens care compositions. Examples of such additional components include buffering agents, cleaning agents, wetting agents, sequestering agents, viscosity builders, tonicity agents, nutrient agents, contact lens conditioning agents, antioxidants, pH adjustors, and the like. These additional components are each included in the present compositions in an amount effective to impart or provide the beneficial or desired property to the compositions. For example, such additional components may be included in the present compositions in amounts similar to the amounts of such components used in other, e.g., conventional, contact lens care products.

Useful buffering agents include, but not limited to, acetate buffers, citrate buffers, phosphate buffers and borate buffers. Acids and bases may be used to adjust the pH of the present compositions as needed.

Useful wetting agents include, but are not limited to, polyvinyl alcohol, polyoxamers, polyvinyl pyrrolidone, hydroxypropyl methyl cellulose and mixtures thereof.

Useful sequestering agents include, but are not limited to, disodium ethylene diamine tetraacetate, alkali metal hexametaphosphate, citric acid, sodium citrate and mixtures thereof.

Useful tonicity adjustors include, but are not limited to, sodium chloride, potassium chloride, mannitol, dextrose, glycerin, propylene glycol and mixtures thereof.

Useful viscosity builders include, but are not limited to, hydroxyethyl cellulose, hydroxypropyl methyl cellulose, carboxymethyl cellulose, polyvinyl pyrrolidone, polyvinyl alcohol and mixtures thereof.

Useful antioxidants include, but are not limited to, sodium metabisulfite, sodium thiosulfate, N-acetylcysteine, butylated hydroxyanisole, butylated hydroxytoluene and mixtures thereof.

The present compositions may be used in the care of a contact lens, e.g., to disinfect the lens, to preserve the lens, to otherwise treat the lens and/or to make wearing the lens safe and comfortable. The present compositions, formulated appropriately, may be used in conventional contact lens care regimens by using the present compositions in place of prior conventional compositions. In many instances, these contact lens care regimens involve contacting the lens with the present composition in an amount, and at conditions, effective to obtain the beneficial or desired contact lens care result. For example, a contact lens to be disinfected may be contacted with a disinfecting composition, e.g., aqueous composition, according to the present invention, preferably at a temperature in the range of about 0°C to about 100°C, more preferably in the range of about 10°C to about 60° C and still more preferably in the range of about 15°C to about 30°C. Contacting at or about ambient temperature is very convenient and useful. The contacting

preferably occurs at or about atmospheric pressure. The contacting preferably occurs for a time to substantially disinfect the lens being treated. Such contacting times can be in the range of about 1 minute to about 12 hours or more.

After this contacting, the disinfected contact lens can be taken from the composition and placed directly in an eye, e.g., a human eye, for safe and comfortable wear. Alternately, after being disinfected, the contact lens can be contacted with a second medium, e.g., a liquid aqueous medium such as a preserved isotonic saline solution, prior to being placed in the eye of the wearer of the disinfected contact lens.

The contact lens care compositions disclosed herein are adaptable for use in most types of contact lens care equipment, such as ultrasonic cleaners and the like.

The following examples are set out to illustrate, but not limit, the scope of this invention.

EXAMPLE 1

The following composition is prepared by blending together the ingredients.

Ingredient	% w/v
Cecropin	5 ppm
PHMB (polyhexamethylene biguanide)	0.5 ppm
Edetate disodium, USP	0.05
Sodium chloride, USP	0.37
Hydrochloric acid	adjust to pH 7.5
Water, U.S.P.	Q.S. to 100%

This composition is formulated as and is effective as a soft contact lens disinfecting composition.

EXAMPLE 2

The following composition is prepared by blending together the ingredients.

Ingredient	% w/v
Cecropin	5 ppm
PHMB (polyhexamethylene biguanide)	0.5 ppm
Hydroxyethyl cellulose, NF	0.65
Sodium chloride, USP	0.67
Boric acid, NF	0.39
Sodium borate decahydrate, NF	0.20
Edetate disodium, USP	0.127
Water, U.S.P.	Q.S. to 100%

This composition is formulated as and is effective as a soft contact lens disinfecting and conditioning composition.

EXAMPLE 3

The following composition is prepared by blending together the ingredients.

Ingredient	% w/v
Cecropin	1 ppm
PHMB (polyhexamethylene biguanide)	0.1 ppm
Hydroxyethyl cellulose, NF	0.65
Sodium chloride, USP	0.67
Boric acid, NF	0.39
Sodium borate decahydrate, NF	0.20
Edetate disodium, USP	0.127
Water, U.S.P.	Q.S. to 100%

This composition is formulated as and is effective as a preserved soft contact lens soaking/conditioning composition

EXAMPLE 4

The following composition is prepared by blending together the ingredients.

Ingredient	% w/v
Defensin	5 ppm
PHMB (polyhexamethylene biguanide)	0.5 ppm
Boric acid	0.39
Edetate disodium	0.1
Sodium chloride	0.40
Sodium borate decahydrate, NF	0.20
Pluronic F-127	0.10
Water, U.S.P.	Q.S. to 100%

This composition is formulated as and is effective as a soft contact lens disinfecting/cleaning composition.

EXAMPLE 5

The following composition is prepared by blending together the ingredients.

Ingredient	% w/v
Defensin	1 ppm
PHMB (polyhexamethylene biguanide)	0.1 ppm
Boric acid	0.39
Edetate disodium	0.1
Sodium chloride	0.40
Sodium borate decahydrate, NF	0.20
Pluronic F-127	0.10
Water, U.S.P.	Q.S. to 100%

This composition is formulated as and is effective as a preserved soft contact lens cleaning composition.

EXAMPLE 6

The following composition is prepared by blending together the various ingredients.

Ingredient	
cyclo [-(Trp-D-Leu)$_3$-Gln-D-Leu]	25 ppm
Sodium chloride	137 mM*
Potassium chloride	2.6 mM*
Sodium hydrogen phosphate	6.4 mM*
Potassium drhydrogen phosphate	1.4 mM*
pH	6.5
Water, U.S.P.	Q.S. to 100%

*Concentration expressed as millimolar.

This composition is formulated as and is effective as a contact lens disinfecting composition. The peptide, cyclo[-(Trp-D-Leu)$_3$-Gln-D-Leu], forms, for example, self

assembles into, antimicrobial peptide nanotubes which penetrate, breach or otherwise compromise the cell membranes of microorganisms, thereby killing the microorganisms.

EXAMPLE 7

A contact lens to be disinfected is immersed in 10 ml of the composition identified in Example 6. The contact lens is maintained in this material overnight, that is for about 12 hours. Afterwards, the lens is removed from the composition, washed thoroughly with a preserved, buffered saline solution and placed in the wearer's eye for safe and comfortable wear. It is found that the above-noted contacting with the composition identified in Example 6 disinfects the contact lens.

EXAMPLE 8

Example 7 is repeated except that after the 12 hour period of time an enzyme-containing tablet is added to the composition. This tablet includes an effective amount of an alkaline material, for example, sodium bicarbonate, and a buffer to increase and maintain the pH of the resulting composition at about 7.5, and a sufficient amount of an enzyme to destroy or degrade (render innocuous) the peptide nanotubes present in the resulting composition. After about 4 hours or until substantially all of the nanotubes are destroyed, the lens is removed from the resulting composition, washed thoroughly with a preserved, buffered saline solution and placed in the wearer's eye for safe and comfortable wear. It is found that the above-noted contacting with the composition identified in Example 6 disinfects the contact lens. The use of the enzyme-containing tablet provides additional insurance that the wearer's eye is not be exposed to active antimicrobial peptide nanotubes.

EXAMPLE 9

Example 8 is repeated except that the enzyme-containing tablet is coated with a delayed release coating and this coated tablet is immersed in the composition identified in Example 6 at the same time the contact lens is so immersed. The coating acts to delay the release of the enzyme-containing tablet in the composition for about 4 to about 8 hours. After the 12 hour period of time, it is found that the contact lens is disinfected and substantially all the antimicrobial peptide nanotubes are degraded. The disinfected lens is removed from the resulting composition, washed thoroughly with a preserved, buffered saline solution and placed in the wearer's eye for safe and comfortable wear.

EXAMPLE 10

Example 7 is repeated except that the composition used includes only 5 ppm of cyclo[-(Trp-D-Leu)$_3$-Gln-D-Leu] and, in addition, includes 0.5 ppm PHMB. It is found that this composition disinfects the contact lens and that, after the lens is washed thoroughly with preserved, buffered saline solution, the disinfected contact lens can be placed in the wearer's eye for safe and comfortable wear.

The present compositions and methods provide very effective antimicrobial activity useful in caring for, for example, disinfecting, contact lenses and in preserving contact lens care products. In addition, this antimicrobial activity is obtained without undue risk of irritating sensitive ocular tissue.

While this invention has been described with respect to various specific examples and embodiments, it is to be understood that the invention is not limited thereto and

that it can be variously practiced within the scope of the following claims.

WHAT IS CLAIMED IS:

1. A method for disinfecting a contact lens comprising:

contacting a contact lens with a liquid medium including antimicrobial peptide nanotubes in an effective contact lens disinfecting amount, thereby disinfecting said contact lens.

2. The method of claim 1 wherein said antimicrobial peptide nanotubes are synthetic, and which further comprises, after said contacting, placing said contact lens in an environment substantially free of said antimicrobial peptide nanotubes prior to placing said contact lens in an eye.

3. The method of claim 1 which further comprises, after said contacting, destroying substantially all of said antimicrobial peptide nanotubes in said liquid medium.

4. The method of claim 3 wherein said destroying step includes placing an enzyme component in said liquid medium in an amount effective to destroy substantially all of said antimicrobial peptide nanotubes in said liquid medium.

5. The method of claim 4 wherein said enzyme component is effective in removing protein-based deposit material from said contact lens in said liquid medium.

6. A combination comprising:

an aqueous liquid medium;

a contact lens in contact with said aqueous liquid medium; and

antimicrobial peptide nanotubes present in said aqueous liquid medium in an amount effective to disinfect said contact lens.

7. A composition useful in disinfecting a contact lens comprising:

antimicrobial peptide nanotubes in an amount effective to disinfect a contact lens in a liquid medium containing said antimicrobial peptide nanotubes; and

a destroying component effective to destroy peptide nanotubes in an amount effective to destroy all of said antimicrobial peptide nanotubes.

8. The composition of claim 7 wherein said antimicrobial peptide nanotubes are synthetic and which further comprises a barrier component in an amount effective to prevent the release of said destroying component in a liquid medium for a period of time sufficient to allow the disinfection of a contact lens placed into a liquid medium containing said antimicrobial peptide nanotubes at the same time said destroying component and said barrier component are placed into the liquid medium.

9. The composition of claim 7 which further comprises an aqueous liquid medium and includes an effective amount of an ophthalmically acceptable pH buffer component.

10. A method of disinfecting a contact lens comprising:

contacting a contact lens with a liquid medium including a combination of a first antimicrobial component selected from the group consisting of antimicrobial peptides and mixtures thereof, and a second antimicrobial

component other than said first antimicrobial component, said combination being present in an effective contact lens disinfecting amount, thereby disinfecting said contact lens.

11. The method of claim 10 wherein said first antimicrobial component is selected from the group consisting of antimicrobial peptides other than synthetic antimicrobial peptide nanotubes, and said second antimicrobial component is substantially non-oxidative.

12. The method of claim 11 which further comprises, after said contacting, placing said contact lens directly from said liquid medium into a mammalian eye.

13. The method of claim 10 wherein said first antimicrobial component is selected from the group consisting of defensins, peptides related to defensins, cecropins, peptides related to cecropins, magainins, peptides related to magainins and mixtures thereof and said second antimicrobial component is selected from synthetic polymeric antimicrobial components and mixtures thereof.

14. A method for treating a contact lens comprising:

contacting a contact lens with a liquid medium including a combination of a first antimicrobial component selected from antimicrobial peptides and mixtures thereof, and a second antimicrobial component other than said first antimicrobial component, said combination being present in an amount effective to preserve said liquid medium.

15. The method of claim 14 wherein said second antimicrobial component is substantially non-oxidative, and said method further comprises, after said contacting,

placing said contact lens directly from said liquid medium into a mammalian eye.

16. The method of claim 14 wherein said first antimicrobial component is selected from the group consisting of defensins, peptides related to defensins, cecropins, peptides related to cecropins, magainins, peptides related to magainins and mixtures thereof and said second antimicrobial component is selected from synthetic polymeric antimicrobial components and mixtures thereof.

17. A composition useful in disinfecting a contact lens comprising:

a liquid medium;

a first antimicrobial component selected from the group consisting of antimicrobial peptides and mixtures thereof; and

a second antimicrobial component other than said first antimicrobial component, said first antimicrobial component and said second antimicrobial component together being present in an amount effective to disinfect a contact lens contacted with said composition.

18. The composition of claim 17 wherein said first antimicrobial component is selected from the group consisting of antimicrobial peptides other than synthetic antimicrobial peptide nanotubes, and said second antimicrobial component is substantially non-oxidative.

19. The composition of claim 17 wherein said first antimicrobial component is selected from the group consisting of defensins, peptides related to defensins, cecropins, peptides related to cecropins, magainins, peptides related to magainins and mixtures thereof, and

said second antimicrobial component is selected from synthetic polymeric antimicrobial components and mixtures thereof.

20. A composition useful for treating a contact lens comprising:

a liquid medium;

a first antimicrobial component selected from the group consisting of antimicrobial peptides and mixtures thereof; and

a second antimicrobial component other than said first antimicrobial component, said first antimicrobial component and said second antimicrobial component together being present in an amount effective to preserve said composition.

21. The composition of claim 20 which is ophthalmically acceptable, and wherein said first antimicrobial component is selected from the group consisting of defensins, peptides related to defensins, cecropins, peptides related to cecropins, magainins, peptides related to magainins and mixtures thereof, and said second antimicrobial component is selected from synthetic polymeric antimicrobial components and mixtures thereof.